tuoslogo_cmy... & SIMCYP BioSim

Day 2: Part 3

PBPK- Mechanistic Models-Allometry

Tuesday 15 April 2008

Using the Knowledge of Biology in the Prediction of Clearance as the Main Determinant of Drug Exposure in Paediatric Populations

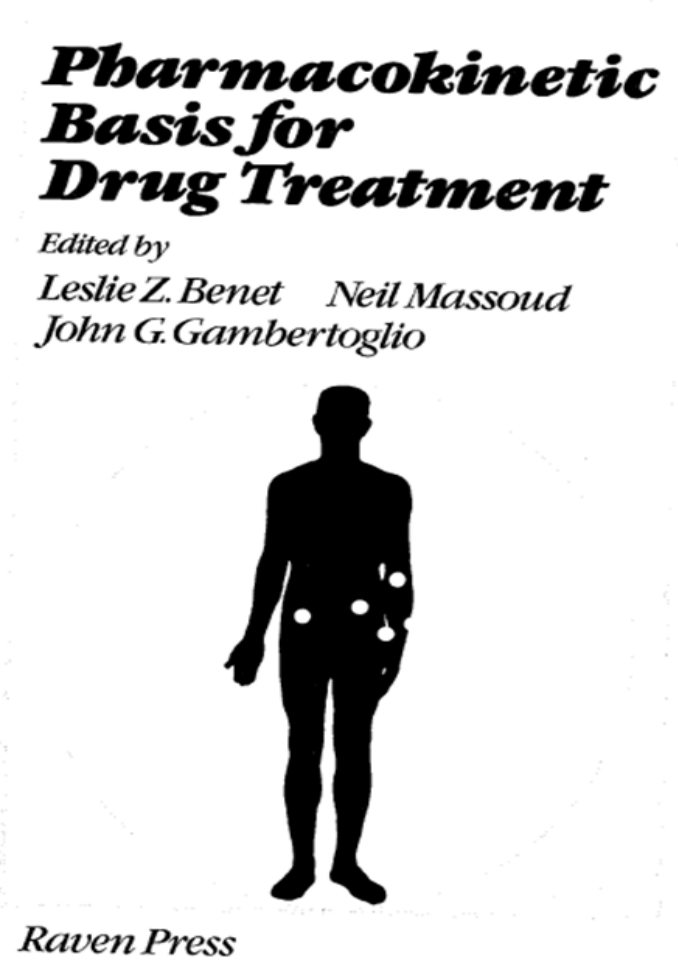
Amin Rostami
Professor of Systems Pharmacology,
University of Sheffield, UK

a.rostami@sheffield.ac.uk)

What Has Changed?

tuoslogo_cmy... & SIMCYP BioSim

1984

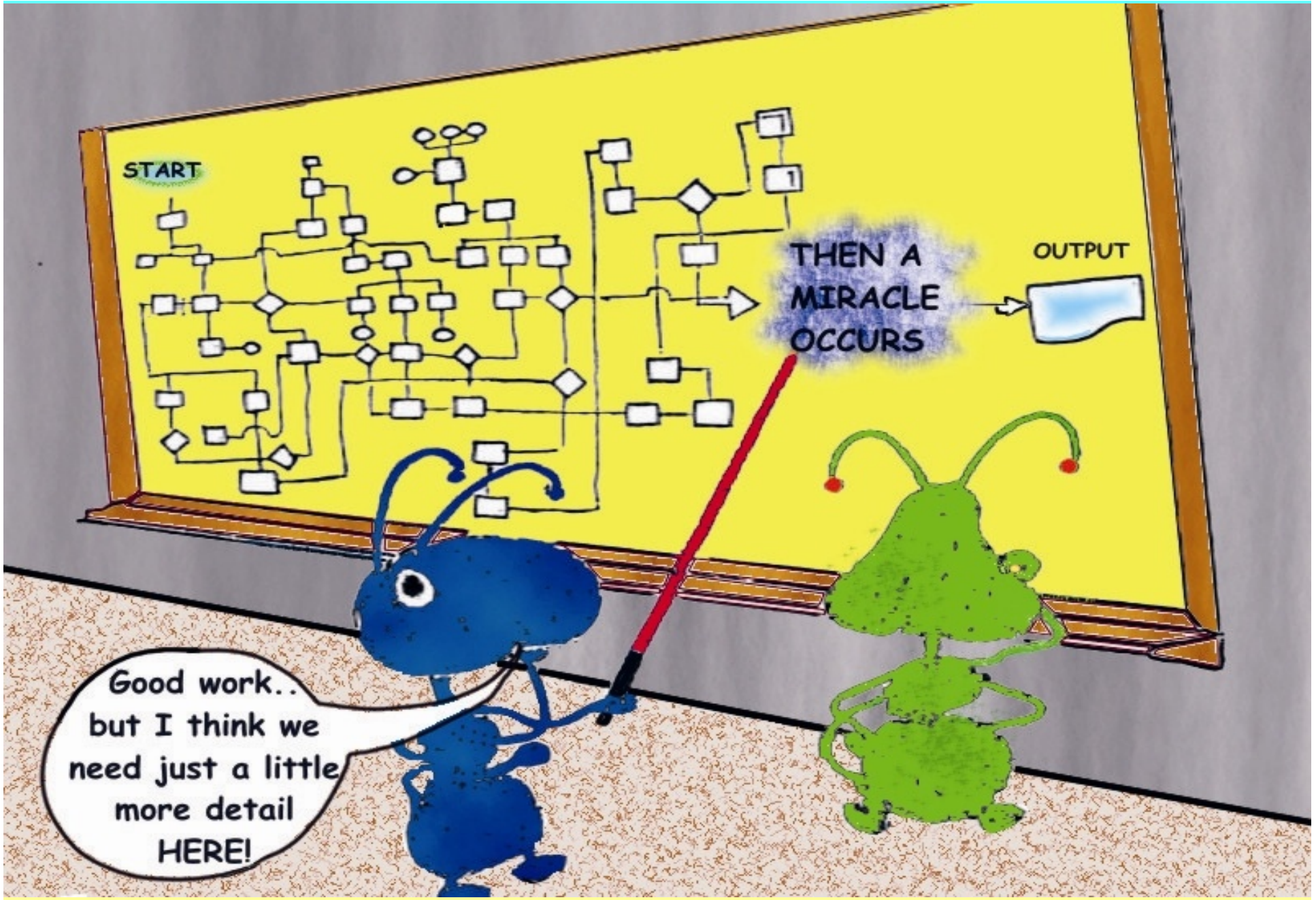


Preface

At any point in history of health care, our knowledge was considered to be quite extensive; however, in perspective, the **knowledge of yesterday seems to have been very limited**, just as today's knowledge can be expected to seem one day as such.

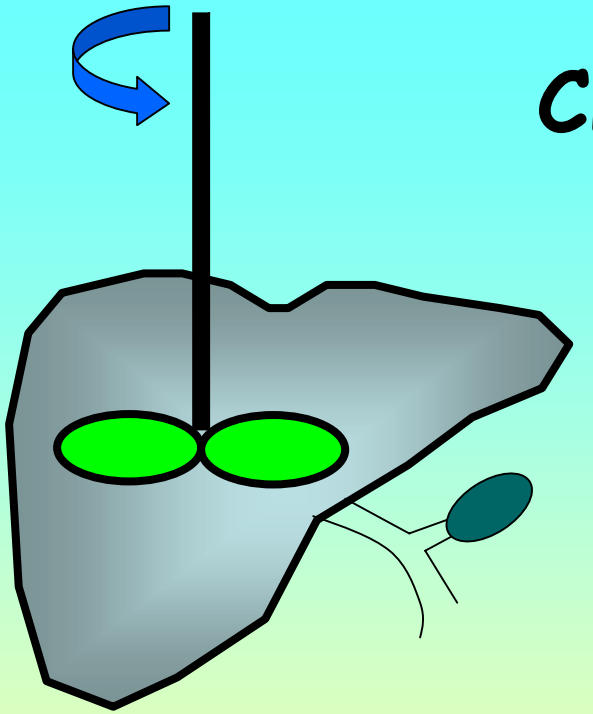
Fundamental in applying basic scientific and mathematical concepts to patient care **is an appreciation of the physiologic constraints placed on these concepts** and appreciation of how disease and/or physiologic changes can further affect these constraints.

A Key Factor: Clarity & Validity of Assumptions



Well-Stirred Liver Model

tuoslogo_cmy... & SIMCYP BioSim



$$CL_H = \frac{Q_H . fu_B . CLu_{int}}{Q_H + fu_B . CLu_{int}}$$

$$F_H = \frac{Q_H}{Q_H + fu_B . CLu_{int}}$$

$$E_H = \frac{fu_B . CLu_{int}}{Q_H + fu_B . CLu_{int}}$$

$Cu_{liver}/C_{total\ (blood)}$

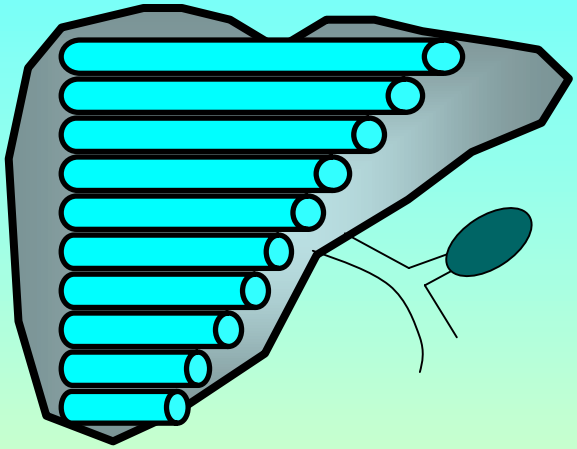
$Cu_{liver}/C_{total\ (blood)} > fu_B$ if drug is substrate for influx transporters

$Cu_{liver}/C_{total\ (blood)} < fu_B$ if drug is substrate for efflux transporters

Parallel Tube Liver Model

tuoslogo_cmy... & SIMCYP BioSim

$$CL_H = Q_H \cdot \left(1 - e^{-\frac{fu_B \cdot CLu_{int}}{Q_H}}\right)$$



$$F_H = e^{-\frac{fu_B \cdot CLu_{int}}{Q_H}}$$

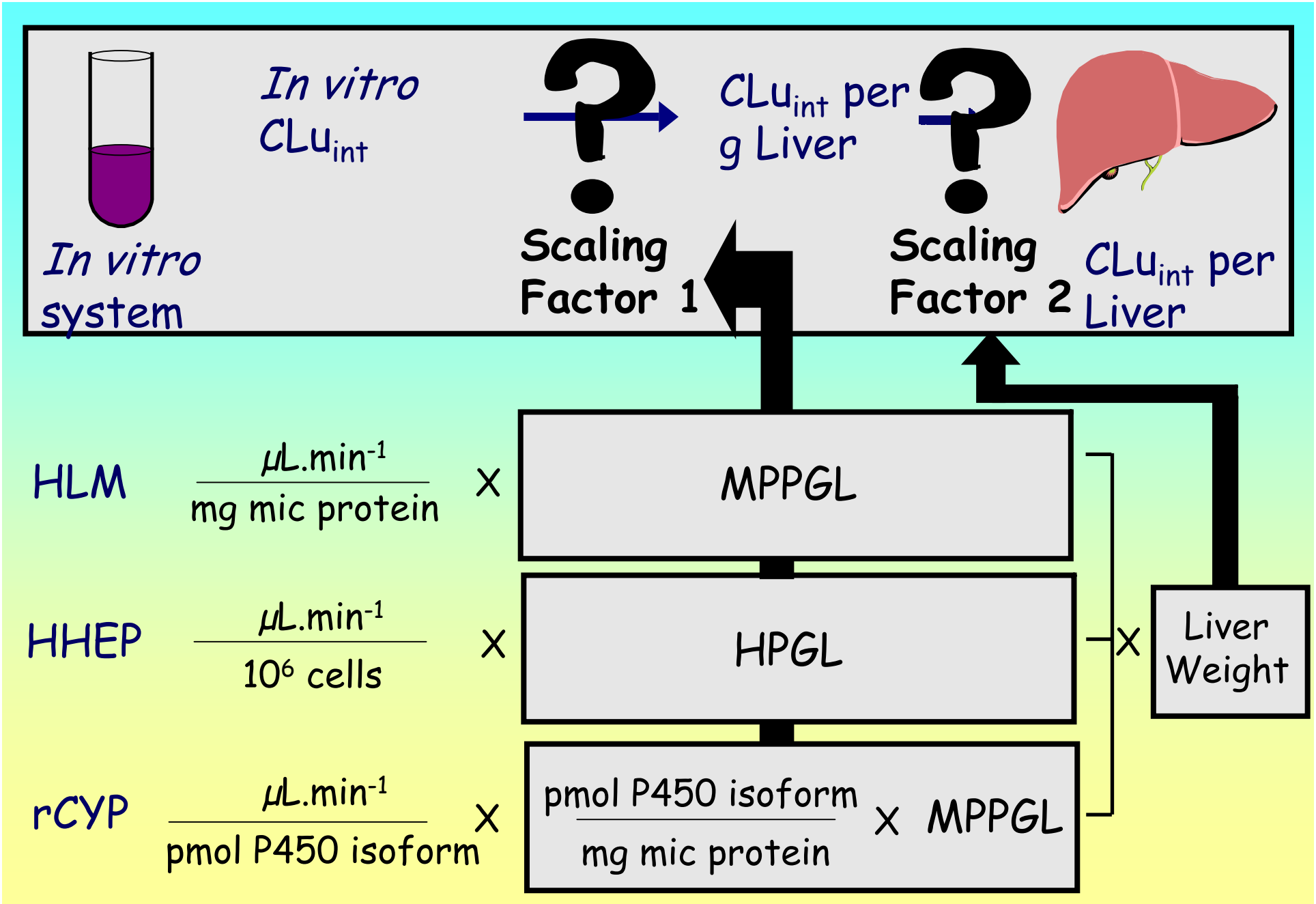
$$E_H = 1 - e^{\frac{fu_B \cdot CLu_{int}}{Q_H}}$$

Dispersion Model

$$CL_H = Q_H \left[1 - \frac{4a}{(1+a)^2 e^{\left[(a-1)/2Dn\right]} - (1-a)^2 e^{\left[-(a+1)/2Dn\right]}}\right]$$

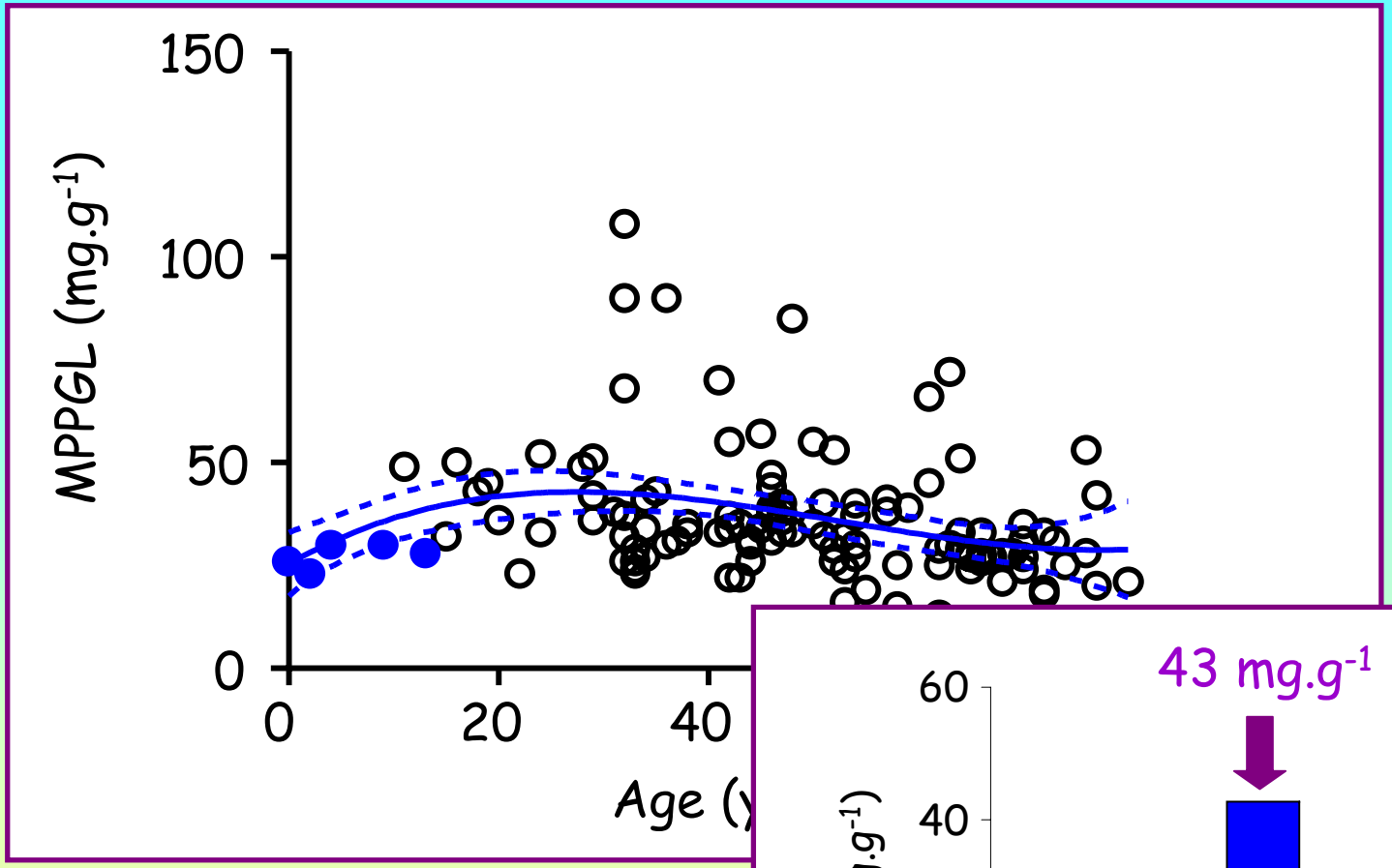
$$a = \sqrt{1 + 4RnDn} \quad ; \quad (\text{e.g.} \quad Dn = 0.17) \qquad Rn = \frac{CLu_{int} \times fu_B}{Q_H}$$

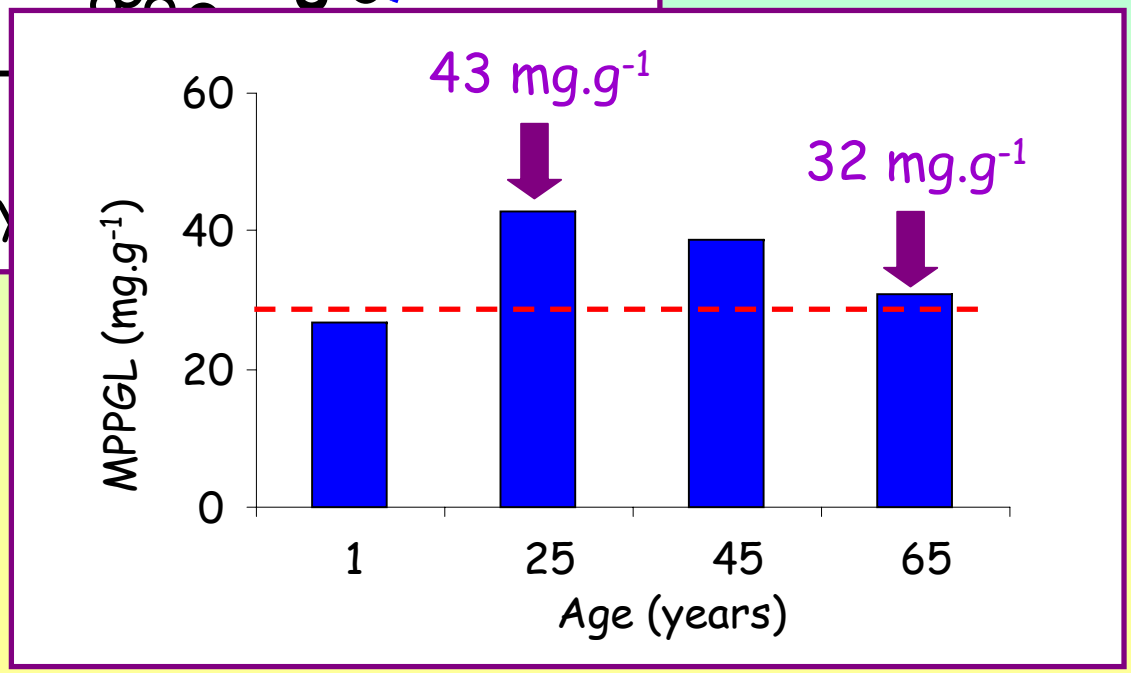
Scaling Factors in Human IVIVE



Non-CYP Related Variation: MPPGL and Donor Age

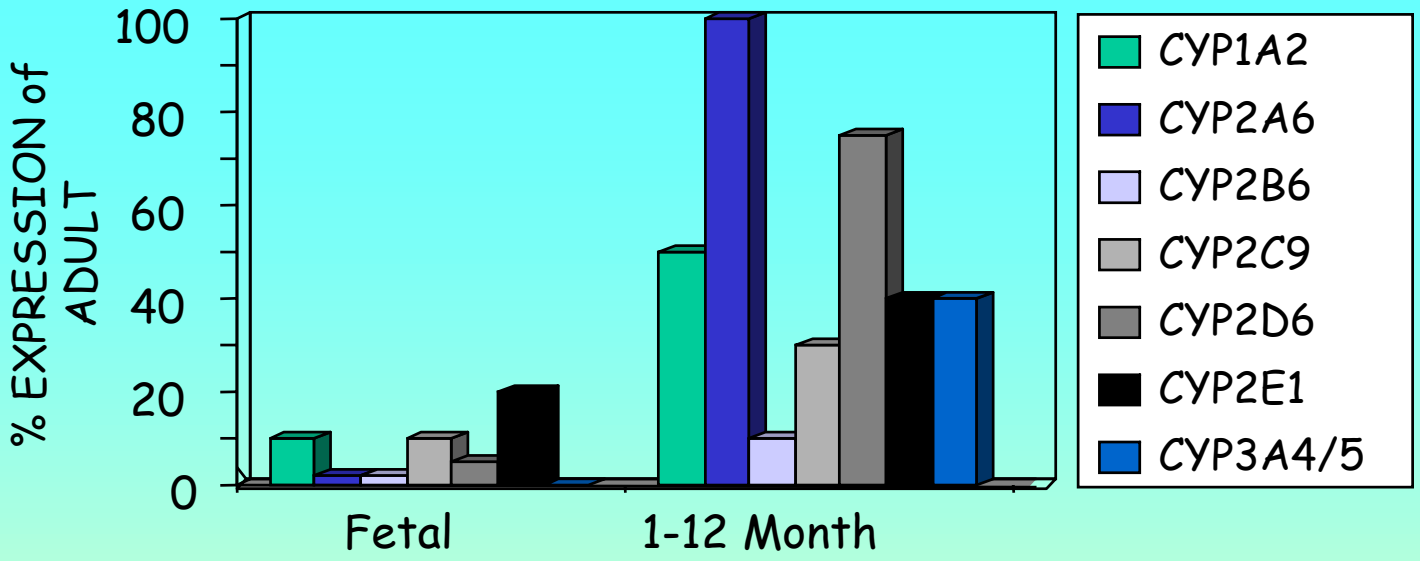
tuoslogo_cmy... & SIMCYP BioSim

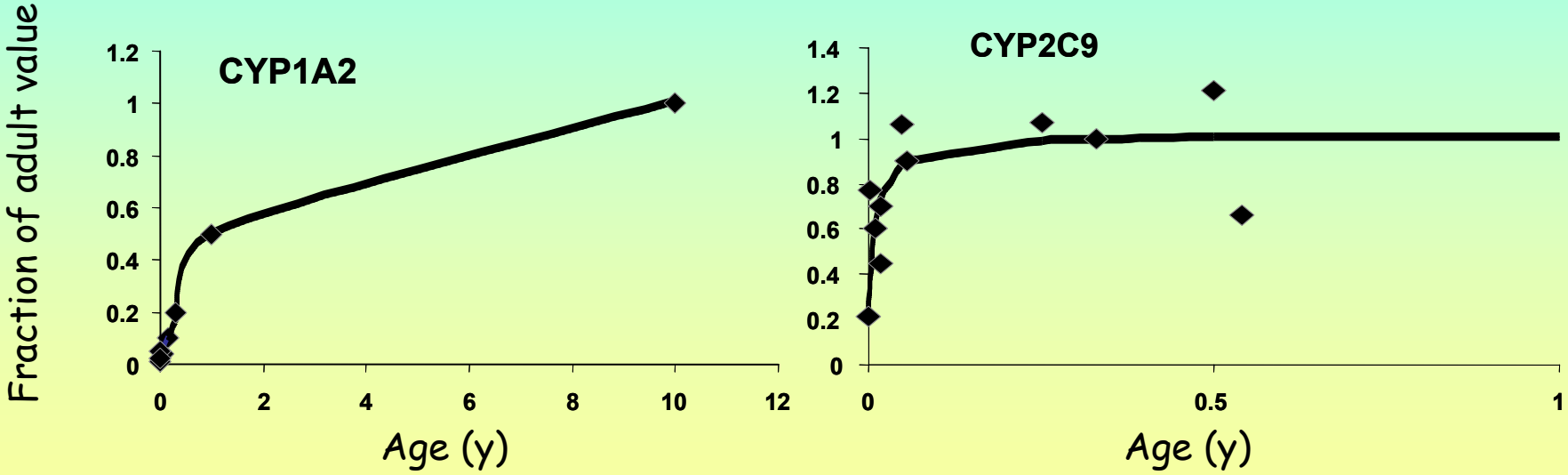




Barter et al. 2007 Curr Drug Met
Barter et al. 2008 Submitted

Development of CYP: Abundance





Some enzymes negligible at Birth but some are not; thus any modelling should consider baseline activity at birth.

Rate per pmol of "Each Enzyme"

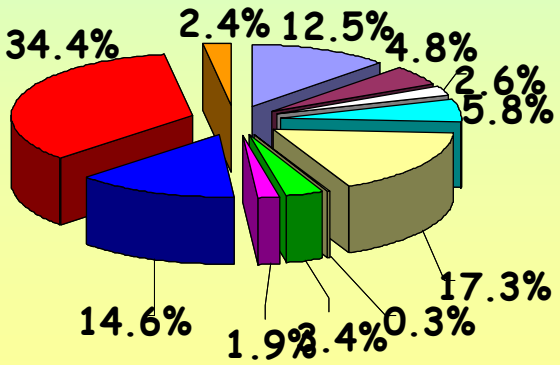
tuoslogo_cmy... & SIMCYP BioSim

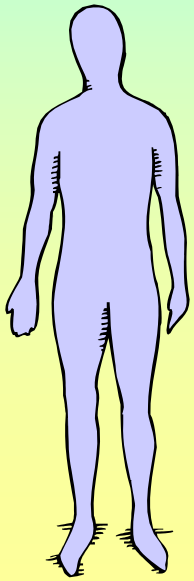
- The abundance of each CYP isoform per mg of microsomal protein
- The relative activity of the isoform(s) responsible for metabolism
- The microsomal protein per gram of liver
- The size of liver Liver Volume = 0.722.BSA $^{1.176}$ (L/m^2)

$$CL_h[L/h] = \left[\sum_{j=1}^{n}\left(\sum_{i=1}^{n}\frac{Vmax\,(rCYP_j)_i \times CYP_j abundance}{K_m\,(rCYP_j)_i}\right)\right] \times MPPGL \times Liver\ Weight$$

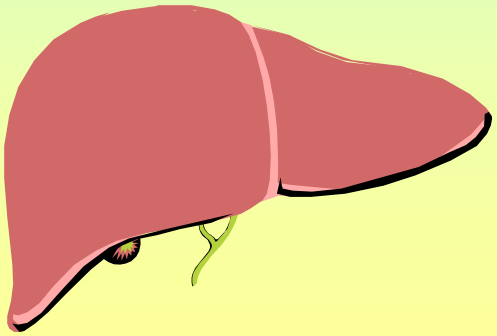
Adults

Proctor *et al.* Xenobiotica 2004





Paediatrics



Liver Blood Flow & fu_B

tuoslogo_cmy... & SIMCYP BioSim

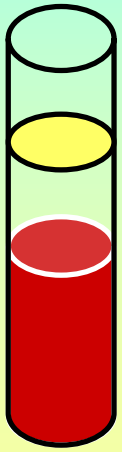
Proportion of cardiac output

22% and 7% for portal vein and arterial liver blood supply, respectively)

Cardiac output based on BSA and age

(2.5, 4, 3 and 2.4 L/min/m^2 for 1, 10, 20 and 80 years of age, respectively)

$$fu_B = \frac{fu}{C_B/C_p}$$



$$C_B/C_p = (C_{RBC}:C_P)*HC + (1 - HC)$$

Min (C_B/C_p) = 1 - Hematocrit

Max $(C_B/C_p) = \infty$

HC & Age: - Children

See Commentary by:

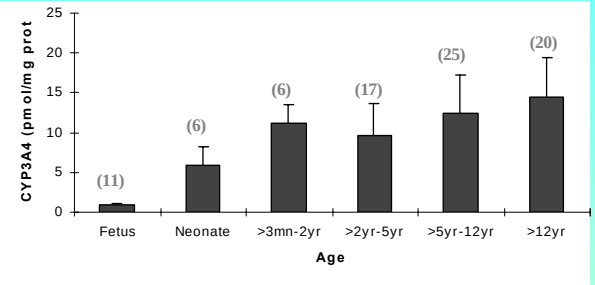
Yang et al. (2007) Drug Metabolism Disposition, 35(3): 501-502

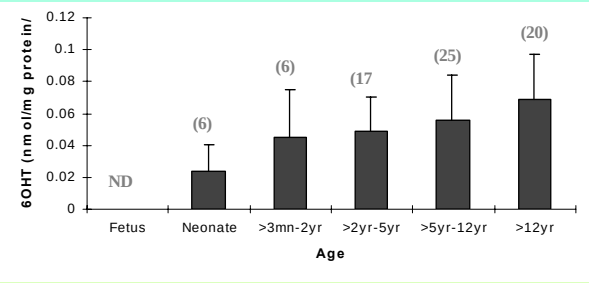
Intestinal Drug Metabolism (CYP3A)

tuoslogo_cmy... & SIMCYP BioSim

Adult CYP3A = 70,000 pmol/intestine

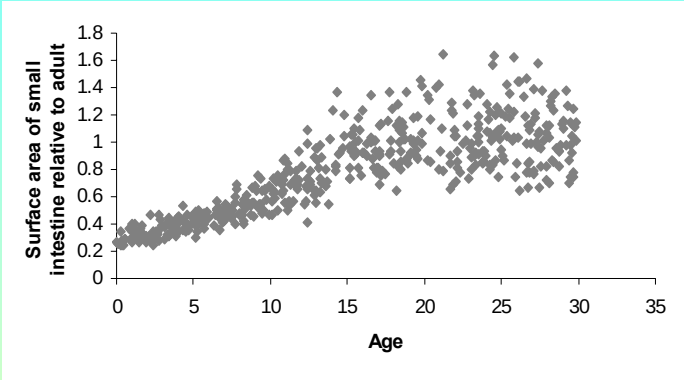
Expression and activity of Intestinal CYP3A with age





+

Relative Gut surface area (Duodenum/ Jejunum)



+ $CLu_{int} = \frac{V_{max}}{Km}$

$$E_g = \frac{fu_{gut} \times CLu_{int-gut}}{Q_{gut} + fu_{gut} \times CLu_{int-gut}}$$

Drug specific parameter related to permeability

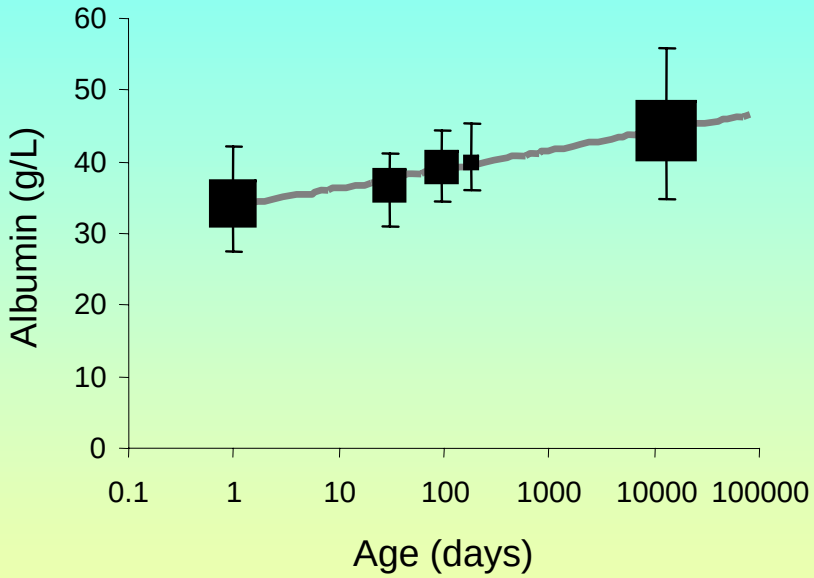
Gut Metabolism / Permeability Model

Age Related Protein Binding

tuoslogo_cmy... & SIMCYP BioSim

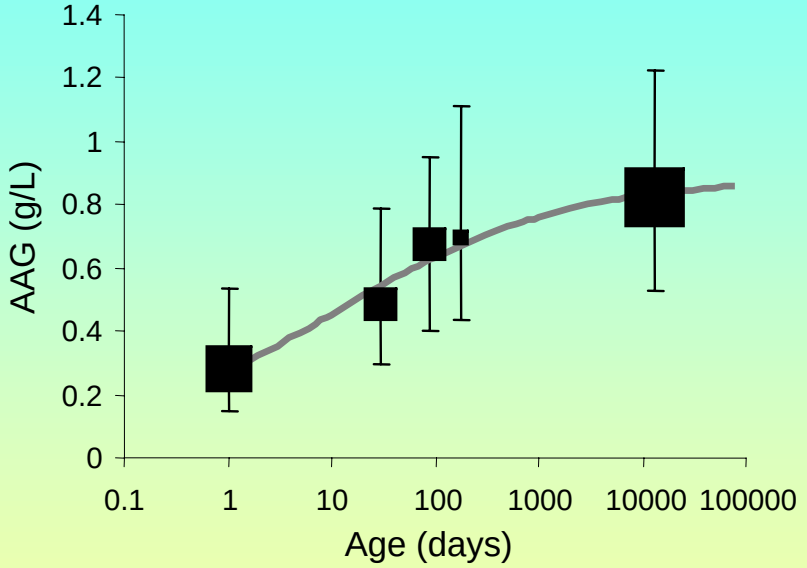
Serum Albumin & Age

Alb = 1.1287Ln(t) + 33.746



Serum AAG & Age

$$AAG_{g/L} = \frac{0.887 \times Age_D^{0.38}}{8.89^{0.38} + Age_D^{0.38}}$$

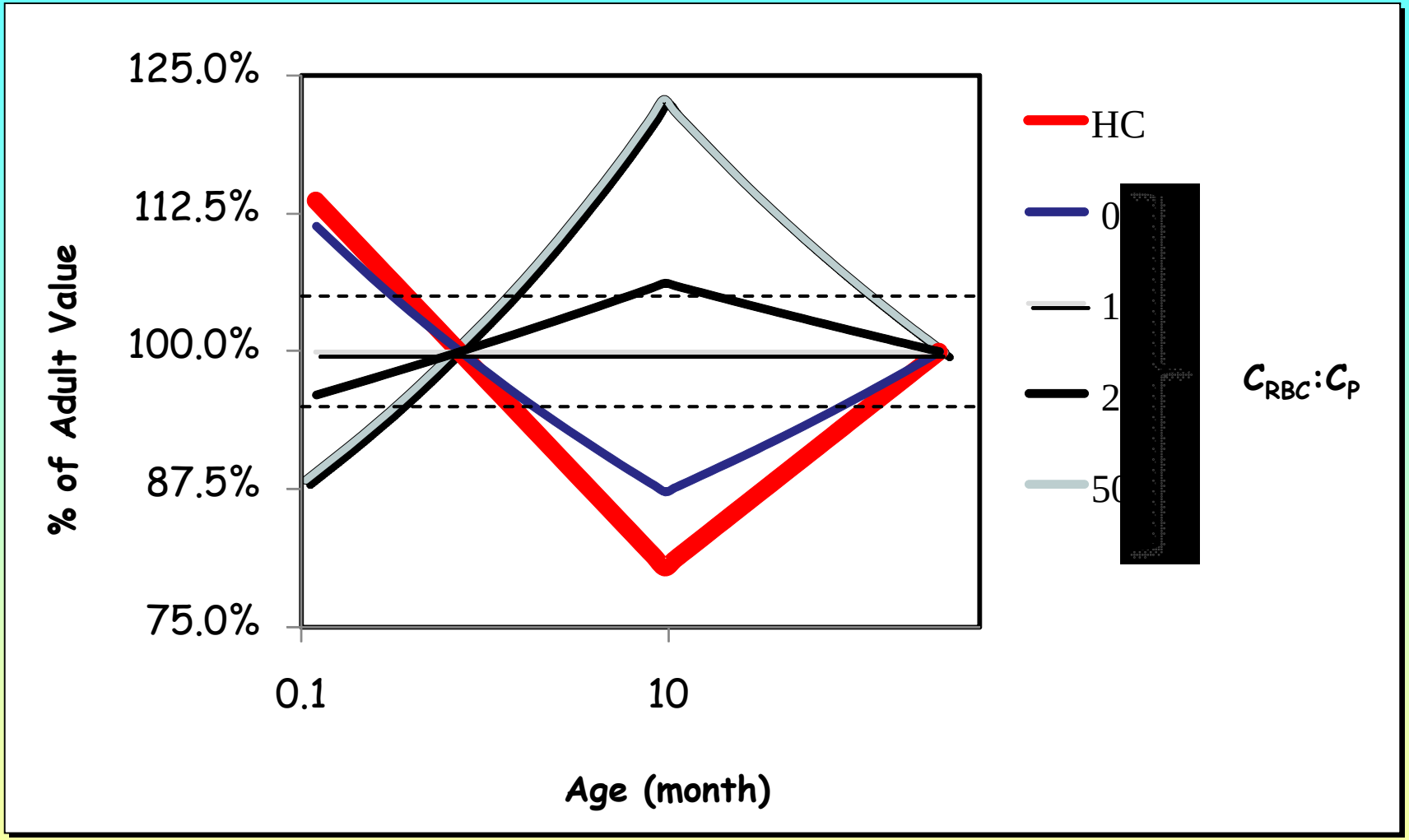


In the absence of changes in dynamics of binding:

$$fu_{neonate} = \frac{1}{1 + \left[\frac{[P]_{neonate}}{[P]_{adult}} \times \frac{(1 - fu_{adult})}{fu_{adult}} \right]}$$

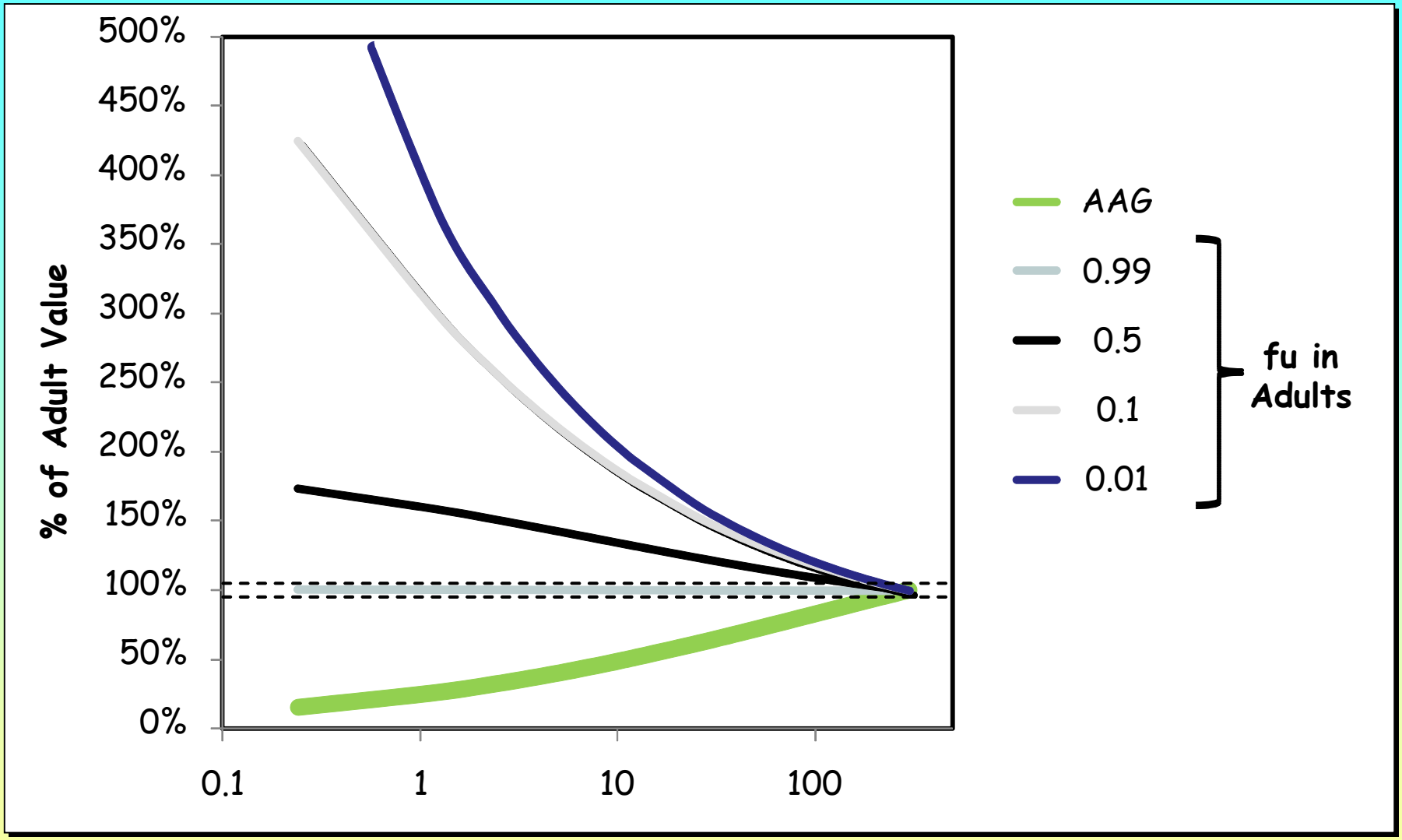
Drug Dependent Influence of Plasma Proteins on CL

tuoslogo_cmy... & SIMCYP BioSim



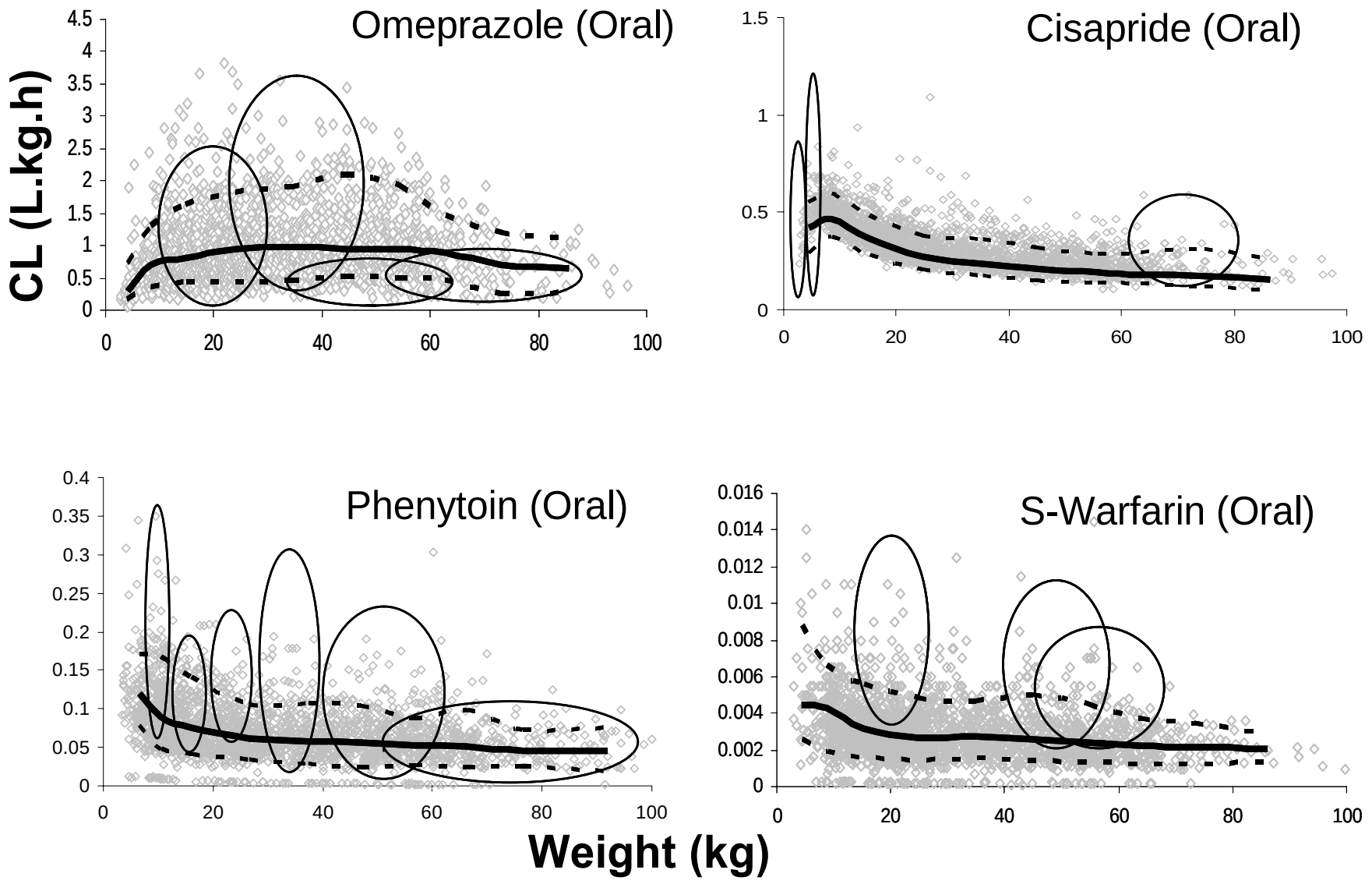
"Drug Dependent" Influence of Haematocrit on CL

tuoslogo_cmy... & SIMCYP BioSim



Non-Monotonic Drug Dependent CL/kg with Age

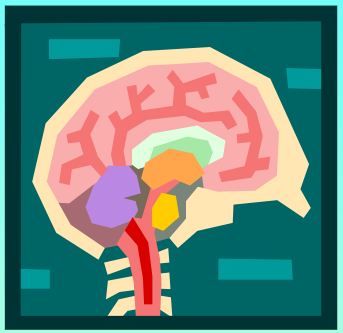
tuoslogo_cmy... & SIMCYP BioSim

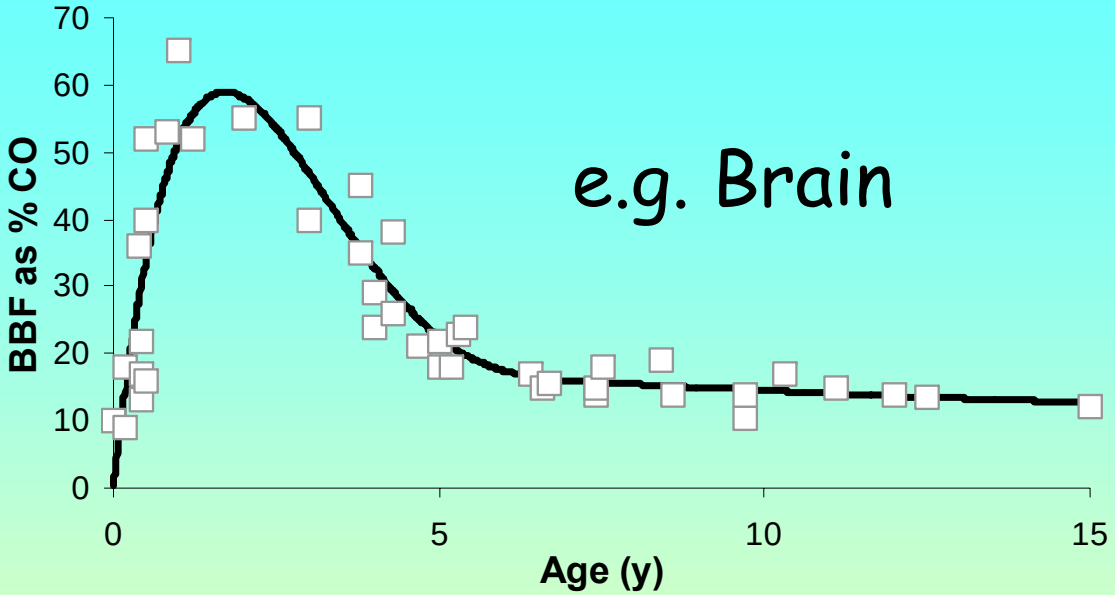


Organ Blood Flows & Tissue Composition

tuoslogo_cmy... & SIMCYP BioSim

- Known changes in blood flow & tissue composition with age



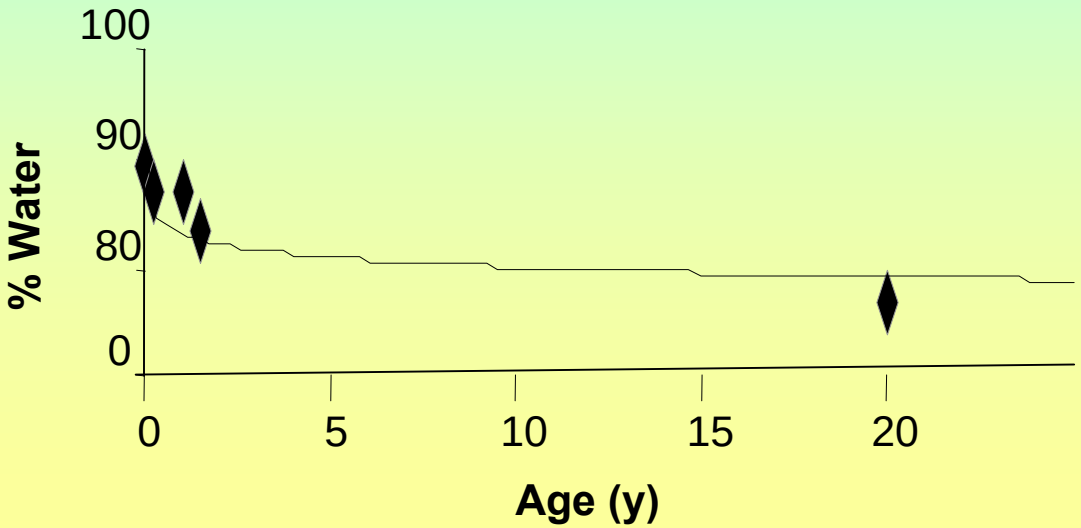


Questions?

- CL vs CLu

- PK in plasma vs PK in Organs

- True PD vs Apparent PD



Knowledge of System Could Describe Observed Data

tuoslogo_cmy... & SIMCYP BioSim

Ontogeny of Dextromethorphan *O*- and *N*-demethylation in the First Year of Life

MJ Blake[1], A Gaedigk[1], RE Pearce[1], LR Bomgaars[2], ML Christensen[3,4], C Stowe[5], LP James[5], JT Wilson[6], GL Kearns[1,7] and JS Leeder[1,7]

Clin Pharmacol Ther 2007

CYP2D6 activity was detectable and concordant with genotype by 2 weeks of age, showed no relationship with gestational age, and did not change with post natal age up to 1 year.

However: we know that:

$$DM/DX \approx \frac{CLu_R}{CLu_{int.DX}}$$

Thus, the development of renal function from birth may change in parallel with the development of the enzyme such that the drug/metabolite ratio may be relatively constant !!!!

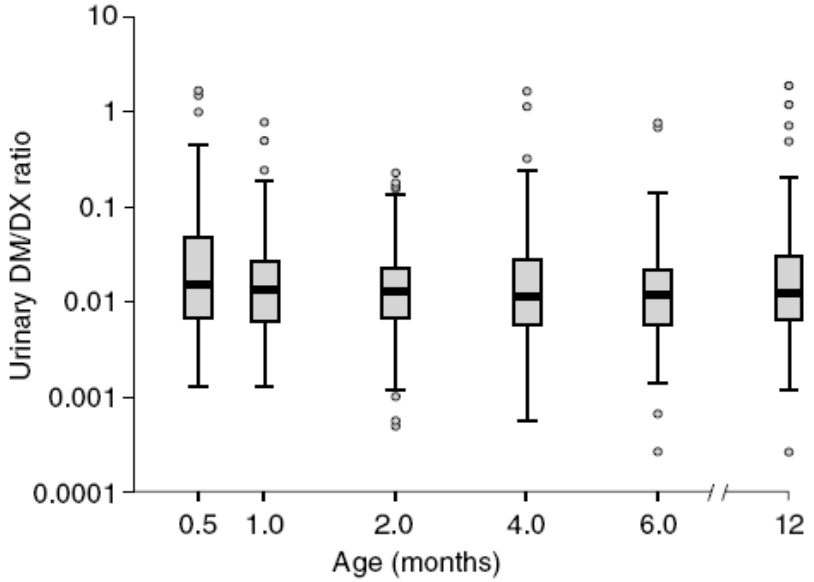


Figure 3 Effect of post-natal age on CYP2D6 activity. Boxplot of the logarithm of DM/DX as a function of post-natal age. Boxes are interquartile range; bars are medians. Whiskers represent the 10th to 90th percentile. ○Outlying values between 1.5 and 3 box lengths from the interquartile range.

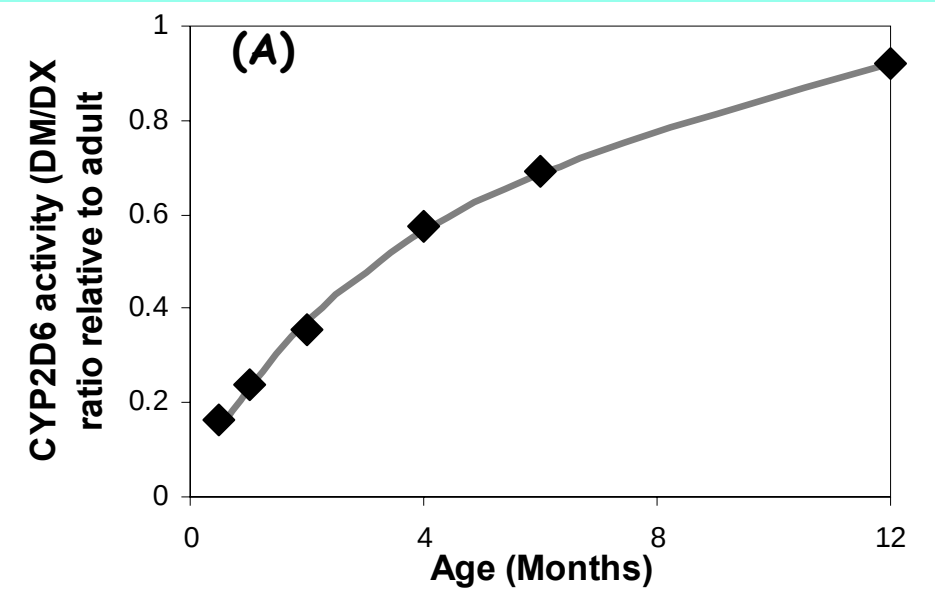
Bottom-Up Approach Meets Top-Down Analysis (1):

tuoslogo_cmy... & SIMCYP BioSim

Development of CYP2D6 and CYP3A4 in the First Year of Life

TN Johnson[1], GT Tucker[1,2] and A Rostami-Hodjegan[1,2]

Clin Pharmacol Ther 2008



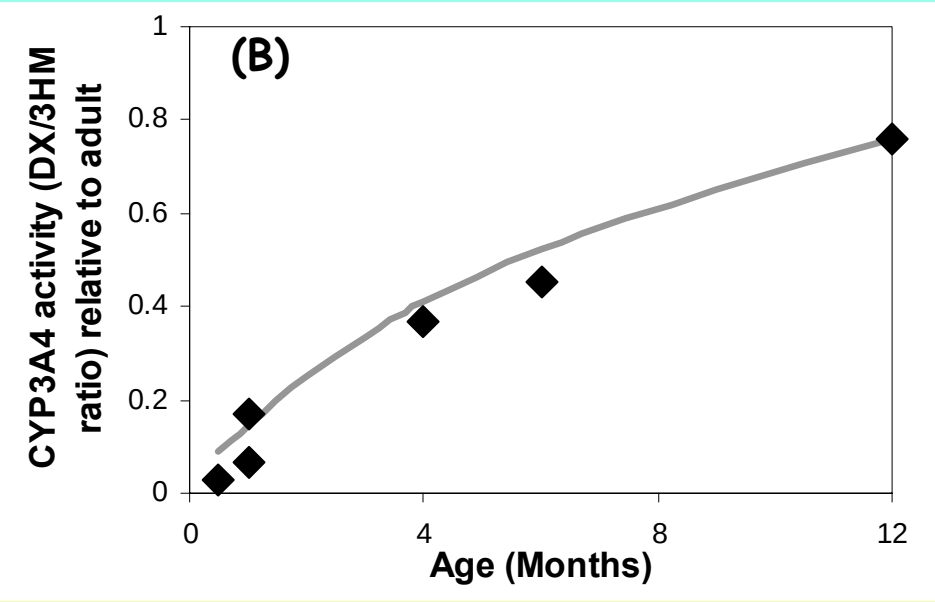
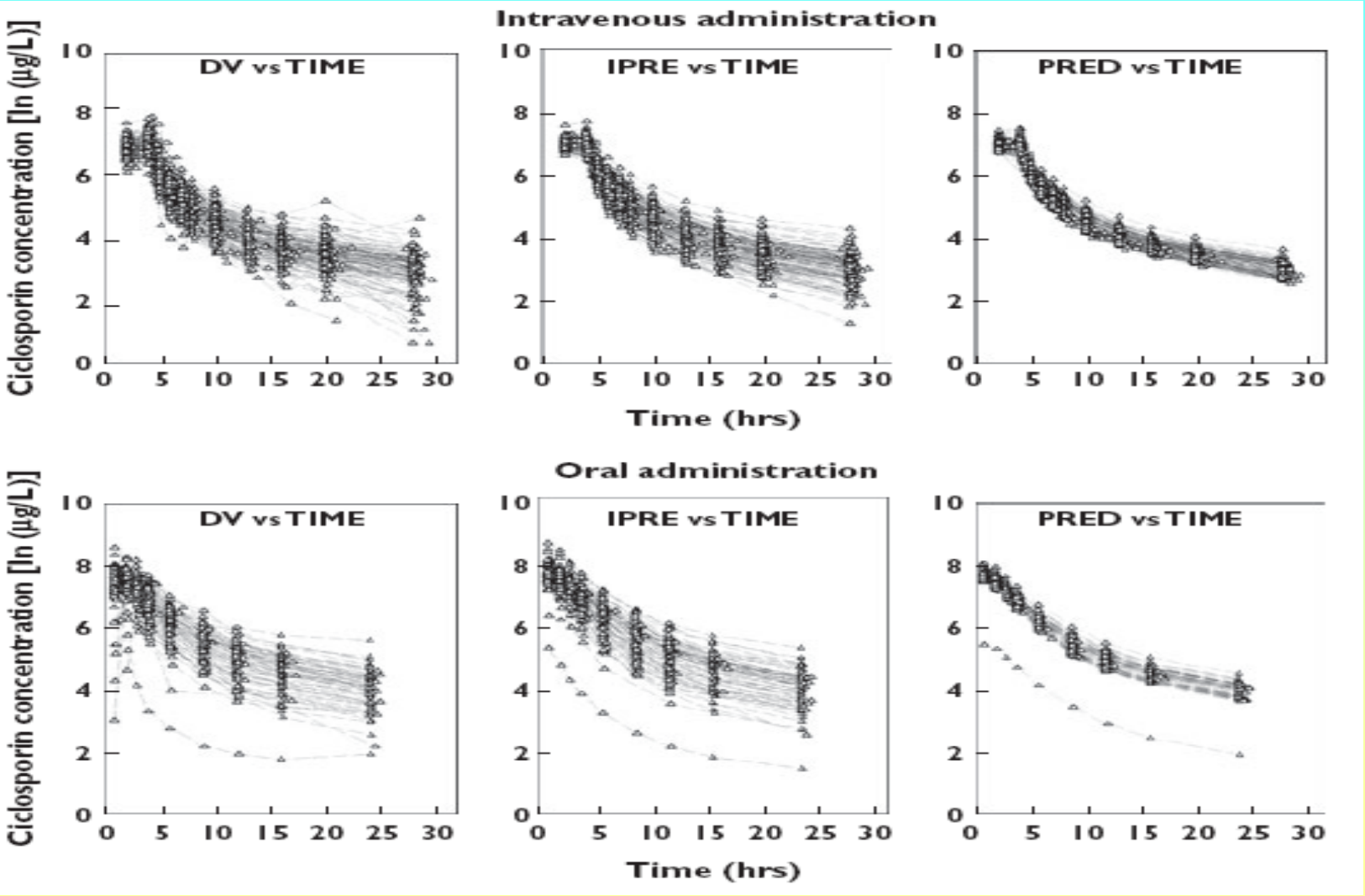


Figure 1. Changes in CYP2D6 (a) and CYP3A4 (b) activity relative to adult values. The data of Blake *et al*, corrected for the development of renal function, are indicated by the diamonds. The simulated change in in the activity of each enzyme (solid line) was derived from *in vitro* data on hepatic enzyme expression and increase in liver weight with age.

tuoslogo_cmy... & SIMCYP BioSim

Sometimes obvious (what to look for and also to see the effect): Example



tuoslogo_cmy... & SIMCYP BioSim

Sometimes obvious (what to look for and also to see the effect):

Example

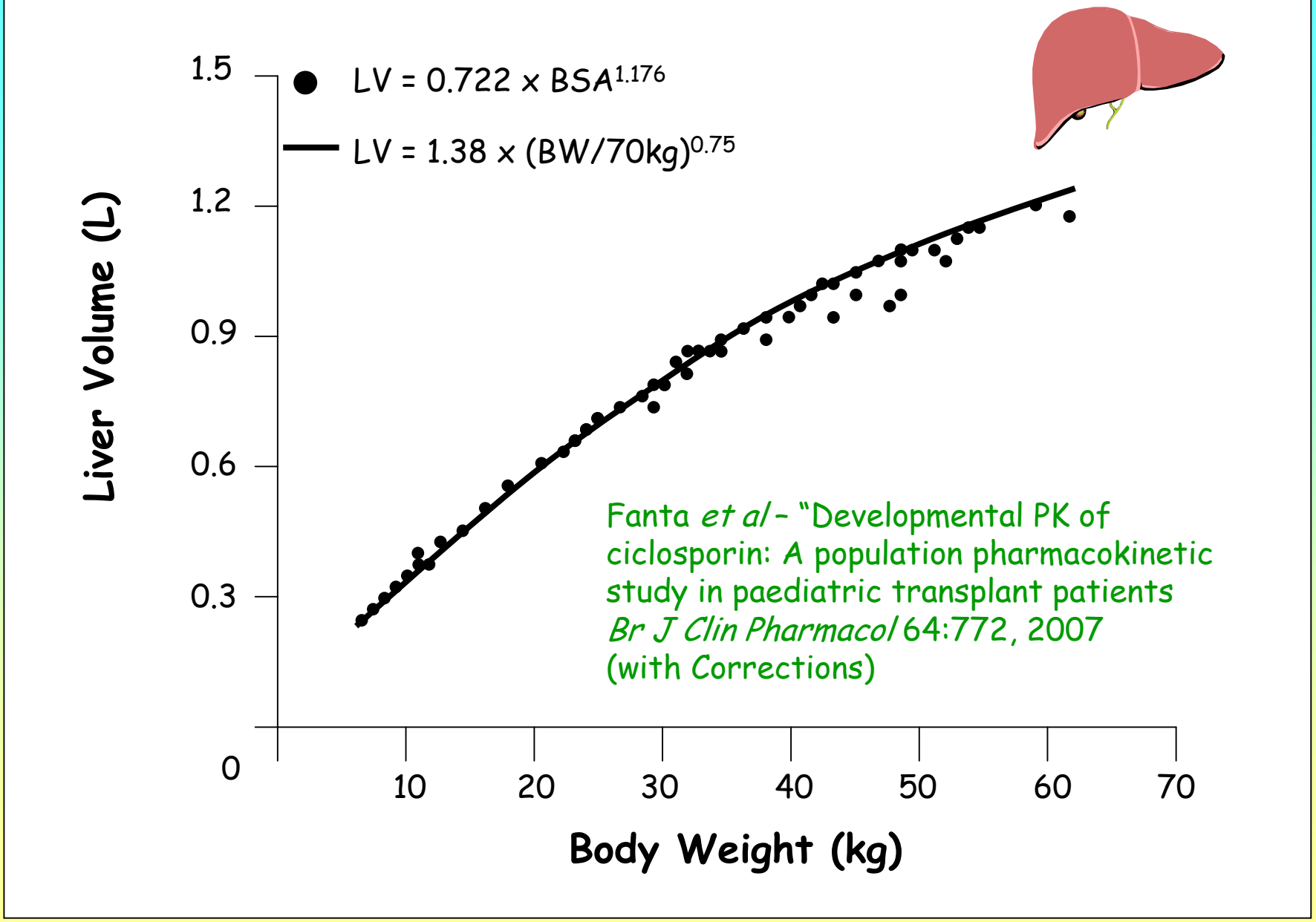
Developmental pharmacokinetics of ciclosporin – a population pharmacokinetic study in paediatric renal transplant candidates

S. Fanta,[1] S. Jönsson,[2,3] J. T. Backman,[1] M. O. Karlsson[3] & K. Hoppu[1,4]

$$CL = \text{Typical parameter estimate} \times (\text{Body weight}/13)^{3/4} \times [1 - 0.0542 \times (\text{Cholesterol} - 5.4)] \times [1 - 0.00732 \times (\text{Haematocrit} - 31)] \times [1 + 0.000214 \times (\text{Serum creatinine} - 524)]$$

The typical values refer to a patient with a body weight of 13 kg, cholesterol of 5.4 mmol l^{-1}, serum creatinine of 524 mmol l^{-1} and a haematocrit of 31%, according to the following covariate model:

Bottom-Up Approach Meets Top-Down Analysis (2):



Bottom-Up Approach Meets Top-Down Analysis (3):

tuoslogo_cmy... &

$[1 - 0.00732 \times 100^{*}(HC - 0.31)]$

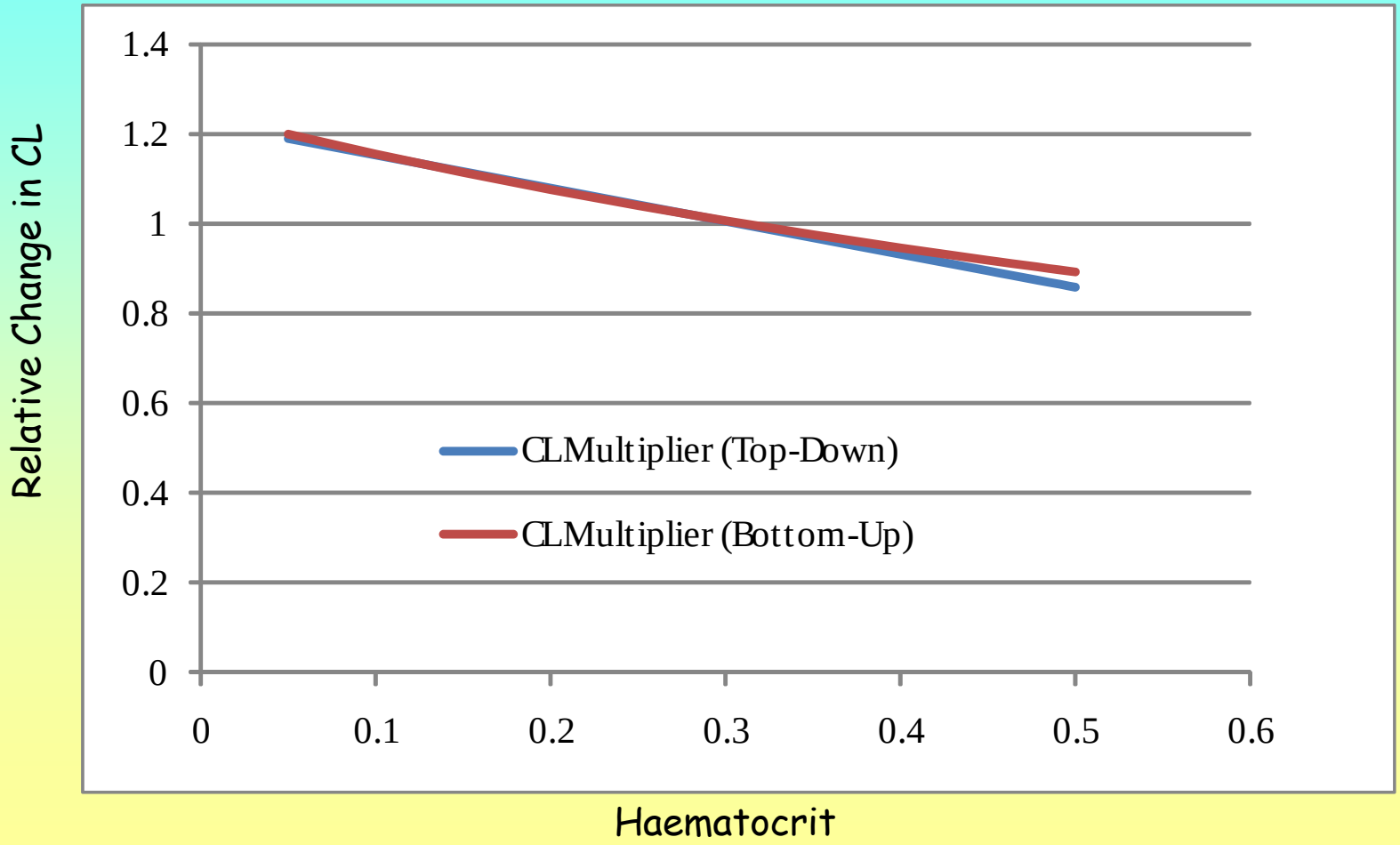
$CLpo \propto fu_B.CLu_{int}$

$CLpo \propto fu/[(C_{RBC}/C_p)^{*}HC + (1- HC)]$

$fu = 0.037$ and $C_{RBC}/C_p = 1.8$

$fu_B = 0\ 0.0296$ (at $HC = 0.31$)

$[[0.037/[1.8^{*}HC + (1- HC)]\ ]/\ 0.0296]$



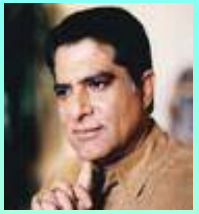
Moving Away from Traditions: Take Hone Messages

tuoslogo_cmy... & SIMCYP BioSim

POP-PK and using drug specific data is a useful tool in studying PK in paediatrics however there are many "advantages" in application of system information (human body) which are often neglected when investigating paediatric pharmacology.

(1) The definition of insanity is – Doing the same thing over and over again but expecting a different result.

Deepak Chopra

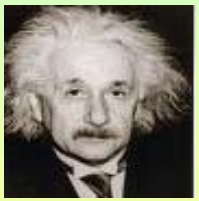


(2) All Models Are Wrong, but Some Models Are Useful !

George EP Box 1987

(3) Everything should be made as simple as possible, but not simpler.

Albert Einstein



(4) Science is built of facts as a house is built of stones; but an accumulation of facts is no more science than a pile of stones is a house.

Henri Poincare, 1902